

## SPECIAL INTEREST GROUP ON NEUROETHICS

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Senior Medical Advisor  
to the  
Assistant Secretary for  
Planning and Evaluation

US Department of Health  
and Human Services

on: Human Subject Protection and Financial Conflicts of Interest

re.: Questions for Comment

Dear Dr. Nightingale,

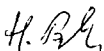
The SIG Neuroethics of the European Federation of Neurological Societies (EFNS) can now officially endorse the statement sent to you previously on Sept. 5/6, 2000 by its secretary, H. Baumgartner.

We include the final version of our position (correction of spelling mistakes; minor clarifications); this will also be sent by e-mail as attachment. The original will be forwarded by air-mail.

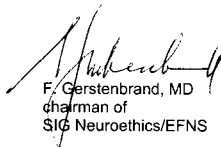
This statement is in the process of being formally endorsed by the World Federation of Neurology (WFN). You will be notified as soon as possible.

With best regards,

Sincerely,



H. Baumgartner, MD  
secretary of  
SIG Neuroethics/EFNS



F. Gerstenbrand, MD  
chairman of  
SIG Neuroethics/EFNS

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### Re.: Comments on „HUMAN SUBJECT PROTECTION and FINANCIAL CONFLICTS of INTEREST“

To whom it may concern

On behalf of the SIG „Neuroethics“ of the European Federation of Neurology we would like to submit the following comments.

Coming from an international scientific neurological organization this comment will address mainly international and transcultural aspects of the topic concerned.

### The USA has to face the global ethical challenges of today's globalized research environment

Today, medical research takes place in a globalized research environment. For clinical drug trials specific standards are in force for the 3 parties of the ICH-agreement, i.e. the USA, EU and Japan. In fact most countries of this world will have to comply with the standards of the 3 biggest markets. Because the problem of „Human Subject Protection and Financial Conflicts of Interest“ is a global problem in a globalized world of clinical trials, global solutions must be found. Whatever is decided in the USA will also affect others world-wide. Therefore the American position should be harmonized – at least with its ICH-partners - taking into consideration the Council of Europe's recent Convention on Human Rights and Biomedicine.

Drug trials in a globalized setting imply that the competition for industry sponsored drug trials and the money associated with these trials is taking place on a world-wide basis. The competition is no longer between individual investigators, or IRB against IRB, or institution against institution, the competition is now on between countries and even regions of this world. When one party raises its standards, trials will simply move to the least demanding sites. These forces will be very hard to control. There is danger that standards will erode. This could happen for example, if the data from a clinical drug trial in an impoverished country – e.g. the data from testing an antiepileptic drug – are accepted by the FDA or by the European agency EMEA:

- i) The patients, the trial subjects, in this country would – in all likelihood not get first class diagnosis and treatment without this clinical trial;
- ii) the investigator's fee – modest to western standards – is more than 1 year's salary of the medical doctor;
- iii) as a consequence everybody is extremely compliant, the data are complete, everything is perfectly recorded and on time;
- iv) as soon as the trial is finished the drug supply is discontinued;
- v) when the drug is finally registered, this poor country will not be able to buy the drug in the foreseeable future – it will be too expensive;
- vi) this is „exportation of risk“ contravening the principle of „justice“.

Having patients from poor countries taking risks for the benefit of wealthy populations reveals a financial conflict of interest of international dimensions and is surely a blatant violation of the principle of „justice“ according to the Belmont report. Trading the patient's risks for the financial or similar benefits of the local investigator or the institution is in itself highly unethical. These examples should remind us of H.K. Beecher's comments on „situation ethics“ in his statement during a 1971 US-senate hearing (S.J. Res. 75; November 9, 1971): „A considerable number of individuals are in the unhappy and really untenable position of accepting the results of unethical experimentation while disapproving the means“. And citing Kant he adds: “ We can say with Kant that people must always be treated as ends, never as means alone.“ (see also: Article 2/Convention on Human Rights and Biomedicine). There are certainly better ways of giving aid than by exporting risk.

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Obviously these sorts of ethical conflicts and dilemmas can hardly be controlled at the local level where they occur. However, the USA and the EU are on record for emphasizing human rights issues when dealing with economic agenda. This is an example where US policymakers and their agencies (e.g. FDA) could improve the observation of important bioethical principles and basic human rights. Not responding to this challenge can entail risks for the wealthy recipients also. Considering that the life-expectancy for males in the above example is about 58 years, it can be highly problematic to use the drug in a country where the average male life expectancy is about 73 years. This could be seen as „re-exportation“ of risk.

### Who should deal with financial relationships or financial conflicts of interest (Questions # 3-6) ?

If financial conflicts of interest or financial relationships affect the investigator, the IRB and/or the institution, they are – at least vis a vis the potential trial subjects - in a situation comparable to a drug company. Except for phase I trials with volunteers e.g. it seems unacceptable to have patients take part in a drug trial at the drug companies own facilities.

However treating the investigator and/or the institution with financial interests at stake like a commercial drug company would solve many problems. All the appropriate rules and regulations are in place and well known. Like a commercial sponsor these investigators or institutions have to find independent and suitable investigators to conduct their trials. If inadequate support is available at the institution conducting the trial, arrangements with industry (drug company; CRO) are certainly possible. This solution would also avoid putting undue burden on the IRBs. Nevertheless, the IRB should always receive the written assurance that no financial conflicts of interest exist (investigator, institution).

The IRB of an institution with financial involvement in the trial could – if necessary - ask another IRB to take over.

In order to encourage compliance 21 CRF Part 54 should apply for investigators with financial interests at stake. In addition, the respective institutions would have to provide appropriate information about their situation. The penalties provided for in 21 CRF Part 54 should suffice to ensure compliance. Active involvement would also put pressure on the institutions to improve oversight and make them accountable.

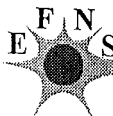
A further advantage is that these adjustments should be acceptable to the ICH-partners and could easily be integrated into the existing ICH-GCP guidelines and related instruments.

### Financial disclosure of investigator's fee and/or financial reward for the institution

ICH-GCP treats the informed consent process exhaustively in 21 paragraphs and sub-paragraphs (4.8.1-4.8.11; 4.8.10: a-t). An additional 10 paragraphs and sub-paragraphs (4.8.11-4.8.15; 4.8.14: a-e) provide guidance, „when subjects can only be enrolled in the trial with the consent of the subject's legally acceptable representative“. Not surprisingly, informed consent documents of 8-10 pages are no longer a rarity.

Taking advice from H.K. Beecher (see above) - „Valid consent – a goal toward which we must strive but rarely attain in any complete sense“ – it is very unlikely that the informed consent process will be enhanced or clarified by adding financial information and/or statements about financial conflicts of interest to an already overburdened document.

However, information about the fee or compensation for the investigator and/or the institution can be useful for the IRB decision and continuous oversight of the trial. The ICH-GCP



European Federation of  
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guidelines don't consider this point although the EU-GCP guidelines address it in chapter 1 point 1.6: „The Ethics Committee should be asked to consider the following“ ..... and further in litera f) „the extent to which investigators and the subject may be rewarded/compensated for participation“

The fact that this stipulation concerning the investigator has been dropped and does not appear in the ICH-GCP guidelines indicates that the parties responsible for these ICH-guidelines – the US, EU, Japanese negotiators – agreed to not make financial disclosure concerning the investigator an obligatory part of the IRB/Research Ethics Committee review process. However, information of this nature is already required and handled by many IRBs. As recent events have shown, it can be important for the IRB to have all the necessary information available. It should not be difficult to convince the ICH-partners to (re-)introduce the disclosure statement from the EU-GCP- into the ICH-GCP- guidelines in the name of transparency.

### Patients not able to consent:

In order to improve diagnosis and treatment of neurological patients with a reduced or absent capacity to consent it can be necessary to include these patients in clinical trials. Different countries have found different solutions for obtaining proxy consent from the subject's legally acceptable representative. However, it would be particularly difficult to burden a person who has to take difficult decisions on behalf of a next-of-kin, with the complex issues of financial conflicts of interest. These conflicts should be solved at another level of decision-making.

Summing up, science is international – a shared treasure of humanity, clinical drug trials have gone global and so have financial conflicts of interest. The investigator, the IRB and institutions view these problems from a local – at most – from a national perspective.

It is therefore up to the political representatives to make sure that the values of our societies - human rights – are being properly observed in a globalized research environment.

**H. Baumgartner, MD**  
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